CREOSOTE HUMAN RISK CHARACTERIZATION

Background

Creosote is a fungicide, insecticide, and sporicide used as a wood preservative for above and below ground wood protection treatments as well as for treating wood in marine environments. All 16 Creosote products currently registered are Restricted Use Pesticides; 15 are End-Use Products and 1 is a Manufacturing-Use Product for formulating industrial end-use wood preservative products. Creosote wood preservatives are used primarily to pressure treat railroad ties/crossties (represents close to 70% of all Creosote use) and utility poles/crossarms (represents 15 - 20% of all Creosote use). Assorted Creosote-treated lumber products (e.g., timbers, poles, posts and groundline-support structures) represent the remaining uses for this wood preservative. The industry refers to different blends of creosote, based on the wood treatment standards set by the American Wood-Preservers' Association (AWPA), as P1/P13 and P2. Typically, railroad ties/crossties are treated with a P2 blend, which is more viscous than the P1/P13 blend used for treating utility poles.

Creosote is applied by occupational handlers only. Since it is a restricted-use pesticide that can only be applied by certified applicators or someone under their direct supervision, it is not available for sale to or use by homeowners. On September 29, 2003, in accordance with section 6(f)(1) of FIFRA, as amended, EPA issued a Notice of Receipt of Requests by Registrants of Pesticide Products containing Creosote to voluntarily cancel non-pressurized and/or to amend to terminate non-pressurized use of affected products.

The Antimicrobials Division (AD), Office of Pesticide Programs (OPP), U.S. EPA, has evaluated the toxicological database for P1/P13 and P2 creosote and determined that the data are adequate to support a reregistration eligibility decision.

Hazard Profile

The Toxicology database for Creosote is adequate to assess the hazard profile of creosote for use in a Preliminary Risk Assessment (PRA). Review of the database shows concern for the mutagenicity and carcinogenicity of creosote as well as cardiomyopathy after inhalation exposure and dermal inflammation after repeated dermal exposure. Results of developmental toxicity testing of creosote in experimental animal species shows qualitative evidence of susceptibility from creosote , thus raising concern for creosote as a potential developmental toxicant.

Cardiotoxicity was observed in a subchronic inhalation toxicity study in rats with the P1/P13 blend of creosote (MRID # 43601001). Diffuse myocardial degeneration affecting the right side of the heart as well as arterial medial hypertrophy of the small arterioles of the lung were observed after 13 weeks of exposure to 0.049 mg/L creosote. Exposure to the P2 blend of creosote by inhalation resulted in changes to the olfactory epithelium (inflammation, hyperplasia, metaplasia).

Follicular cell hypertrophy of the thyroid was also observed as well as increased thyroid weight. Both blends produced granular pigment deposition within the lungs, a s shown by the presence of granular pigment within the alveolar macrophages. In 90-day dermal toxicity studies with both blends of creosote, these effects were not observed, although a significant dermal response (inflammation) was observed for both blends.

The developmental and reproductive toxicity of creosote was evaluated. Developmental toxicity studies in the rat with both blends showed qualitative evidence of susceptibility to offspring. For the P1/P13 blend, significantly increased resorptions and post-implantation loss as well as decreased live fetuses per litter were observed at a dose of 175 mg/kg/day, while the only maternal effect at this dose was increased incidence of hair loss. In addition, increased incidence of cardiovascular, vertebral, and digital malformations was observed which exceeded both concurrent and historical control incidence. For the P2 blend, single incidences of malformations of the skull and eye were considered treatment related, in the absence of maternal toxicity. A developmental toxicity study in rabbits with P1/P13 creosote showed increased abortions, decreased number of live litters, and decreased mean implantation sites at a dose of 75 mg/kg/day in maternal rabbits. There were no significant effects on fetuses from treated dams at any dose level. A 2-generation reproduction study using P1/P13 Creosote showed decreased pre-mating body weights in F1 female rats and F1 males rats at a dose of 25 mg/kg/day, the lowest dose tested in this study. At 25 mg/kg/day and above there was reduced fertility and pregnancy indices in the F1 generation in comparison to controls, but the control fertility index was also lower than expected. Thus although there was no evidence of susceptibility in this study, the low fertility and pregnancy indices for F1 female parental animals introduced uncertainty in the interpretation of the results in treated animals.

Although there are no current Agency guideline neurotoxicity studies available for creosote, the existing studies on creosote indicate no evidence of neurotoxicity for either the P1/P13 or P2 blends of creosote (ATSDR, 2002). Based on the above, and realizing that creosote is currently registered only for non -food use and is a restricted use pesticide, no additional neurotoxicity testing will be required at this time.

In consideration of the available evidence that creosote is a positive mutagen, the Agency waived the requirement for the standard mutagenicity battery, and instead required dominant lethal testing of both the P1/P13 and P2 blends. The results of testing of both the P1/P13 blend and P2 blend of creosote showed that, at doses toxic to the dosed animals (330.5 mg/kg for the P1/P13 blend, and 194 mg/kg for the P2 blend), there was no evidence of a dominant lethal effect of either creosote blend.

As there are no existing tolerances or other clearances for residues of creosote in food, an FQPA assessment is not necessary. Potential post-application exposures to residents, including children (e.g., from use of railroad ties by homeowners), could not be assessed due to lack of exposure data. The available evidence on developmental and reproductive effects of creosote was assessed by the Health Effects Division (HED) Hazard Identification Assessment Review Committee on

April 1, 1999 The committee expressed concern for potential infants and children's susceptibility of creosote, based on the severity of offspring vs. maternal effects observed with testing of creosote in the P1/P13 blend developmental toxicity study in rats at the 175 mg/kg/day dose level as well as deficiencies observed in the 2-generation reproduction toxicity study in rats.

A large body of experimental evidence exists which shows a positive relationship between dermal exposure to creosote and development of tumors in experimental animals. In addition to its tumor-promoting potential, the ability of creosote to induce lung tumors after dermal application was examined. Dermally applied creosote (0.25ml undiluted, twice weekly for 8 months) induced 5.8 lung adenomas per mouse in mice housed in stainless steel cages, while untreated controls showed 0.5 lung adenomas/mouse (Roe et al, Cancer Res. 18: 1176-1178, 1958). Carcinogenicity of two high-temperature derived creosote oils was studied by Poel and Kammer (JNCI 18: 41-55, 1957). The light creosote fraction is composed mainly of benzene, toluene, xylene, and solvent naphtha, while the blended oil is composed of creosote oil, anthracene oil, and oil drained from recovery of naphthalene. Oils were applied by drops to the skin of mice at concentrations of 20%, 50%, or 80% three times a week for life. By weeks 21-26, both oils had induced skin tumors. Several mice exhibited metastases to the lungs or regional lymph nodes. Coal tar carcinogenicity was studied by Culp et al. (1996) in which female B6C3F1 mice (48/group) were administered coal tar in the diet at concentrations of 0, 0.01, 0.03, 0.1, 0.3, 0.6, and 1% for 2 years. The coal tar was a mixture of samples from seven waste sites. Tumors of the forestomach were observed in all groups fed the coal-tar containing diet, as were small intestine tumors fed the 0.6% or 1.0% concentrations of coal tar. In a second study by Culp et al. (1998) female B6C3F1 mice were given coal tar samples in the diet, derived from manufactured gas plant waste sites at 0, 12, 33, 117, 333, 739, and 1300 mg/kg/day (coal tar sample 1) or 40, 120, and 346 mg/kg/day (coal tar sample 2) for 2 years. Coal tar sample 1 was a mixture of samples from seven waste sites and coal tar sample 2 was a mixture from two of the waste sites plus a third waste site with a high benzo(a)pyrene content. Significant concentration-related increases in incidence of tumors of the liver, lung, forestomach, and increased incidence of hemangiosarcoma, histiocytic sarcoma, and sarcoma were observed for both coal tar sample 1 and 2. Tumors of the small intestine were also observed in addition in those mice receiving coal tar sample1, similar to the earlier study.

In humans, evidence for carcinogenicity of creosote varies. Several studies have associated occupational exposure to creosote with development of skin cancer, with a latency period of 20-25 years. These studies are very old (1920's to 1940's), when occupational safety practices were much more lax than today. More recent reports (1980) show no increase in risk of skin, bladder, or lung cancer in wood treatment plant workers, or after treatment for 4 years with coal-tar medicinal therapy for treatment of dermatitis. These reports, however, were limited in scope. Those reports associated with therapeutic use of coal tar did not mention the fact that the composition of the coal tar used therapeutically is different than that used for wood treatment. In the report on wood treatment workers, the population studied was small, and the follow-up

period was too short to allow a long enough latency for tumor development.

The carcinogenicity data base submitted to the Agency for creosote consists of a six-month initiation/promotion study of creosote conducted in mice. Creosote in this study was tested both as an initiator (5 dermal applications per week for 2 weeks at doses of 500 μg/mouse, 25 mg/mouse, or 56 mg/mouse followed by TPA for 26 weeks) and as a promotor (DMBA as a positive initiator at 50 μg/mouse followed by twice weekly applications of creosote at the same doses as used for the initiation protocol). As an initiator, creosote did not produce any increase in incidence of benign tumors, but at the 25 and 50 mg doses, squamous cell carcinomas were observed in 2/30 mice at each dose. As a promotor in DMBA-initiated mice, creosote produced dose-related increases in skin papillomas, keratoacanthoma, squamous cell carcinoma, and basal cell carcinoma at the 25 and 50 mg doses. Increases in these tumor types were also observed when creosote was used as both initiator and promotor. This study shows that creosote acts most effectively as a promotor but also functions as a "complete" carcinogen.

The Agency in 1988 acknowledged limitations on conducting a quantitative risk assessment from use of a single component of creosote (Guidance for the Reregistration of Pesticide Products Containing Coal Tar/Creosote As the Active Ingredient, USEPA, 1988), but it was also observed that creosote mixtures are "complex mixtures with known synergistic effects" on carcinogenicity. A specific quantitative risk assessment on carcinogenicity of creosote has not been performed by the Agency, but a cancer slope factor (q*) exists for one of the more prominent components of creosote, benzo(a)pyrene, with a q* value of 7.3 as published in the Agency's IRIS database. The Antimicrobials Division proposes to use benzo(a)pyrene as an indicator for conduct of the cancer risk assessment for creosote. Administration of benzo(a)pyrene by inhalation has been shown to result in respiratory tract tumors, and administration by the dermal route results in skin tumor production, similar to the tumors observed from administration of creosote. Benzo(a)pyrene has also been shown to be a "complete" carcinogen similar to creosote, and also tests positive for mutagenicity in a variety of assays. Cancer risk estimates for oral exposure to polycyclic aromatic hydrocarbon mixtures as well as inhalation exposure to coal tar/pitch condensation aerosol (Schenider et al., J. Appl. Toxicol 22(1), 2002; Heinrich et al., Toxicol. Lett. 72(1-3), 1994) have been performed using benzo(a)pyrene as an indicator. The use of benzo(a)pyrene as an indicator is not felt to be overly conservative and may underestimate carcinogenic risk of creosote, as other components of creosote including naphthalene, 1-methylnaphthalene, carbazole, quinoline, and beno[b]fluoranthene have also shown carcinogenic potential in animal studies (Nesnow et al., Exp. Lung Res. 24(4): 1998; Murata et al., Fundam Appl. Toxicol. 21(1): 1993) and could likely contribute additional potency over that of benzo(a)pyrene alone. While the Agency proposes this approach, the Agency is also aware of the recent study of Culp et al. (1998) that examined tumors induced by coal tar as well as the recent publications by Gaylor et al. (2000) and Schneider et al. (2002) which analyzed these data for purposes of quantitative cancer risk. The Agency is considering these publications and their potential modification of the approach proposed above for quantification of creosote carcinogenicity.

The metabolism of Creosote has not been examined, due to the extremely complex nature of the components of creosote. Information from the Agency for Toxic Substances and Disease

Registry indicates that some of the components of creosote are persistent within the body.

Dose-Response Assessment

On April 1, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicological endpoints selected for occupational and residential (dermal and inhalation) exposure risk assessments for Creosote. On September 3, 2003, the Antimicrobials Division Toxicity Endpoint Selection Committee (ADTC) met to verify the selected endpoints for long-term dermal risk assessments for creosote and inhalation risk assessment, and also discussed whether dermal and inhalation Margins of Exposure should becombined for creosote risk assessment. The toxicological endpoints selected for various exposure scenarios are summarized in the table below.

Table 1 Toxicology Endpoint Selection for Creosote

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute and Chronic Dietary			
		Acute and Chronic Dietary risk assessment not required	
Carcinogenicity (Dietary)	Creosote has been shown to exert positive mutagenic effects in vitro, and has been shown to be positive for carcinogenicity in an initiation/promotion study. Creosote has been classified as a B1 carcinogen in IRIS. Oral cancer slope factor for benzo(a)pyrene, a component of creosote, used as indicator for carcinogenic potential of creosote: 7.3 $(mg/kg/day)^{-1}$ + 50% dermal absorption.		
Short-Term Dermal (1-30 days)	Oral NOAEL=50	decreased body weight gain at 175 mg/kg/day	Developmental Toxicity - Rat
	MOE = 100 (50% dermal absorption)		
Intermediate-term Dermal (1-6 months)	Dermal NOAEL = 40	Decreased body weight gain at 400 mg/kg/day	90-Day Dermal Toxicity Study in the Rat
	MOE = 100		
Long-Term Dermal[a] (>6 months)	Oral LOAEL = 25 mg/kg/day	decreased pre-mating body weight	2-generation reproduction study - Rat
	MOE = 300 (10x, 10x, 3x for use of a LOAEL)		
Inhalation[b] (any time period)	NOAEL = 0.0047mg/L MOE = 100	decreased body weight, body weight gain, altered hematology	90-day Inhalation Study in the Rat
Dermal absorption[c]	50%, estimated from ratio of oral/dermal LOAEL		

[a]after re-examination of the toxicology data, the ADTC concluded that the 2-generation reproduction toxicity study was appropriate for long-term dermal risk assessment for the following reasons: the duration of the 2-generation reproduction study is more representative of the time frame (i.e. long-term) than the 90-day dermal study, and is consistent with OPP policy regarding duration of the study vs. route of exposure; body weight gain decreases in the 2-generation reproduction toxicity study were observed in the F2 generation, supporting the time frame for the long-term endpoint (i.e. > 6 months). The 90-day dermal study effects are not as representative of the time frame for the long-term dermal risk assessment. However, the two studies can be considered co-critical studies for this endpoint. Correction of the LOAEL from the 2-generation reproduction toxicity study for dermal absorption (50%) and use of a LOAEL (3x extra UF) yields a MOE and endpoint (300 and 50 mg/kg/day) similar to the 90-day dermal toxicity study (40 mg/kg/day and MOE of 300 [extra 3x to extrapolate to long-term endpoint]).

[b]the ADTC re-examined the use of the inhalation toxicity study selected for inhalation risk assessment for creosote and concluded that a developmental toxicity study, as used for the oral and dermal risk assessments of creosote, is not appropriate for inhalation risk assessment because: (1) the inhalation toxicity study showed significant effects on body weight gain early in the study (one week) and is therefore relevant for short-term assessment (2) it is also a route-specific study; and (3) the inhalation NOAEL is more sensitive than the developmental NOAEL. Therefore, the inhalation study will remain as the study for the short-term inhalation endpoint.

[C]No dermal absorption studies for creosote are available. The HIARC estimated a dermal absorption of 50% based on the results of an oral developmental toxicity in rats and a 90-day dermal toxicity studies in the same species (rats) with similar endpoints (e.g., decrease in body weight gains). Benzo(a)pyrene has also shown a similar extent of dermal absorption (Ng et al., Toxicol. Appl. Pharamcol. 115: 216-223, 1992) and supports the HIARC's decision for creosote.

An acute and chronic Reference Dose value were not selected for creosote, as there are no food uses for creosote and a dietary risk assessment is not needed.

As there are no existing tolerances or other clearances for residues of creosote in food, an FQPA assessment is not necessary. Potential post-application exposures to residents, including children (e.g., from use of railroad ties by homeowners), could not be assessed due to lack of exposure data. The available evidence on developmental and reproductive effects of creosote was assessed by the Health Effects Division (HED) Hazard Identification Assessment Review Committee on April 1, 1999 The committee expressed concern for potential infants and children's susceptibility of creosote, based on the severity of offspring vs. maternal effects observed with testing of creosote in the P1/P13 blend developmental toxicity study in rats at the 175 mg/kg/day dose level as well as deficiencies observed in the 2-generation reproduction toxicity study in rats.

Human Exposure

Dietary Exposure

Based upon its classification as a restricted use pesticide and restrictions on use sites since 1984, dietary exposure to creosote is not expected through food. In drinking water, the Agency has determined that the use pattern of Creosote is not expected to impact water resources through labeled uses. In light of this finding, EPA believes that Creosote's use will not impact ground or surface water and therefore is not expected to lead to exposure to humans through drinking water.

Non-Dietary Exposure

Occupational uses of creosote are restricted to pressure treatments. To estimate handler and post-application exposure at pressure treatment facilities, the Agency used dermal and inhalation exposure data from a worker exposure study (MRID 453234-01) submitted by the Creosote Council II:

1. This study was designed to estimate the exposure to creosote of individuals performing job functions involved in commercial pressure treatment of lumber, utility poles, and railroad ties at four typical commercial treatment facilities in the United States and Canada (referred to as Sites A through D). Three end use products for coal tar creosote were used. Twenty-five workers and 11 job functions (tasks) were monitored for up to 4 or 5 consecutive work days each (8 hour shifts). Many of the job functions may have been performed by one or more worker(s). Where a single worker performed the duties of more than one job function, the title of the job function which represented the majority of their work efforts was used to identify the worker. Employee positions monitored were: treatment operator, treatment assistant, cylinder area loader operator, cylinder area loader helper, checker, drip pad laborer, load-out area loader operator, load-out area loader helper, load-out area forklift operator, oil unloader, test borer, and water treatment system operator.

2. Dermal and inhalation exposure levels were estimated. Dermal exposure levels were

estimated by passive dosimetry using whole body dosimeters (WBDs) and cloth dosimeter gloves. The WBDs and cloth dosimeter gloves were worn under the workers' protective clothing and chemical resistant gloves. Inhalation exposure levels were estimated by active dosimetry using a sampling train (placed in the worker's breathing zone) that consisted of a PTFE air filter upstream from two in-line XAD-2 resin filled air sampling tubes. The air was pulled through the sampling train by a portable air sampling pump.

3. Creosote cannot be measured directly because it is a mixture of many component compounds. In this study dermal exposure to "total creosote" was estimated by measuring the levels of ten individual polynuclear aromatic hydrocarbon (PNA) compounds. Each analyte was determined in each WBD and glove sample as if it represented total creosote. Inhalation exposure was estimated for 11 individual PNA compounds as well as for benzene-soluble PNAs and related compounds collectively known as coal tar pitch volatiles (CTPVs). The PTFE filter retained the CTPVs, while the PNAs were retained in the XAD-2 resin tubes. (However, there was no attempt by the study sponsors to relate inhalation levels found for PNAs and CTPVs to "total creosote" -- a significant weakness with the study.)

4. The creosote worker exposure study (MRID No. 453234-01) used personal air samplers to determine air concentrations of 11 PNAs in the breathing zone of the workers. The samplers worn by the workers consisted of PTFE filters (2-μm pore size) backed by XAD-2 sorbent tubes. Analyzes were performed for 11 PNAs. Of the 11 PNAs, naphthalene was detected in 100 percent of the samples. Because naphthalene was present in all samples for each of the 12 job classifications, it has been selected to indicate potential risks to workers exposed to creosote.

Potential post-application exposures to residents, including children (e.g., from use of railroad ties by homeowners), could not be assessed due to lack of data.

Risk Characterization Summary

Dietary Risk-food

Based upon its classification as a restricted use pesticide and restrictions on use sites since 1984, dietary risk assessment is is not applicable to currently registered uses of creosote.

Dietary Risk -drinking water

The Agency has determined that the use pattern of Creosote is not expected to impact water resources through labeled uses. In light of this finding, EPA believes that Creosote's use will not impact ground or surface water and therefore is not expected to lead to exposure to humans through drinking water. If new uses are added in the future, the Agency will reassess the

potential impacts of creosote on drinking water as a part of the aggregate risk assessment for this chemical.

Occupational Risk

AD has determined that **Short and Intermediate-term Occupational Handler dermal risk estimates** do not exceed AD's level of concern (i.e. MOEs are greater than 100)

AD has determined that **Chronic Occupational Handler dermal risk estimates** exceed AD's level of concern (i.e. MOE < 300) for the treatment operator. The MOE for the treatment assistant does not exceed the target MOE

For inhalation exposure to creosote, AD has determined that **Occupational Handler Inhalation risk estimates** exceed AD's level of concern (i.e. MOEs < 100) for both the treatment operator and treatment assistant.

Cancer risks from dermal and inhalation exposure exceed the level of 1×10^{-4} for all handler scenarios described.

The results of the post-application occupational exposure and risk assessment indicate that the short-term non-cancer margins of exposure for dermal exposures do not exceed the level of concern for most post-application scenarios with the exception of the oil unloader (MOE=93). Intermediate-term dermal margins of exposure are for most scenarios not of concern with the exception of the cylinder area loader helper, checker, and oil unloader. Long-term dermal margins of exposure are of concern with the exception of the load-out area loader operator and helper. Inhalation margins of exposure were all of concern for all exposure druation (i.e. MOEs less than 100). In addition, cancer risks for all post-application occupational scenarios exceed the level of concern (1E-04); all are greater than 1E-02.

Combined Occupational Margins of Exposure

Separate Margins of Exposure were calculated for dermal and inhalation routes of exposure for occupational scenarios. The Antimicrobials Division's ADTC committee determined that the MOEs for dermal and inhalation exposure should not be combined. First, effects are observed in the 90-day inhalation study that are not observed in the 90-day dermal study and include hematological changes, serum biochemistry, thyroid follicular cell hypertrophy, lesions of the nasal epithelium, and increased absolute and relative liver weights. Only decreased body weight and dermal irritation were observed in the 90-day dermal toxicity study. Thus, MOEs will not be combined for the dermal and inhalation routes of exposure.

Data Needs

There are no additional toxicology data requirements for creosote at this time. However, additional toxicological data requirements may be identified as the PRA is refined. In addition, risk mitigation measures (e.g., engineering controls) need to be discussed with the Creosote Council prior to requiring any potential exposure data for occupational workers. Additional data are needed to assess exposure and risks to railroad workers, utility pole installers, and residential exposure to utility poles and/or railroad ties.

Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider available information concerning the cumulative effects of a particular pesticide's residues and other substances that have a common mechanism of toxicity. As there are no tolerances for creosote, the Agency is not considering whether creosote has a common mechanism of toxicity with any other chemicals. However, based on the complex nature of the creosote mixture, components of this mixture may act in similar ways to produce the adverse effects noted for creosote.

Endocrine Disruption

EPA is required under FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all active pesticides or other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), the EPA has determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC recommendation, that program include evaluations of potential effects in wildlife may. For pesticide chemicals, EPA will use FIFRA and, to some extent that effects in wildlife may help determine whether a substance may have an effect on humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening additional hormone systems may be added to the Endocrine Disruptor Screening Program.

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, creosote may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

Risk Characterization

Overview

Dermal Margin of Exposures (MOEs) - Summary: Toxicological endpoints for short-, intermediate-, and long-term dermal exposures to creosote have been selected A Margin Of Exposure (MOE) of greater than 100 for creosote is considered to indicate no risk concern for short-term (1 day to 1 month) and intermediate-term (1 to 6 months) exposures, and a MOE of greater than 300 for creosote is considered to indicate no risk concern for long-term (6 months or longer) exposures.

Inhalation MOEs - Summary: Toxicological endpoints for short-, intermediate-, and long-term inhalation exposure have been selected for creosote as well as naphthalene. Naphthalene has been selected as an indicator or worker risks because it was detectable in all worker inhalation exposure samples. For creosote, a MOE of greater than 100 is considered to indicate no risk concern. For naphthalene, the Antimicrobials Division used the inhalation reference concentration (RfC) for naphthalene published in the EPA's IRIS database. The RfC was derived from a 2 year chronic inhalation study in the mouse in which exposure was for 6 hours/day, 5 days/week. The ACGIH documentation for recommending the TLV cited the same 2 year mouse study as EPA. However, the RfC value of 0.0031 mg/m^3 differs dramatically from the TLV's 8-hr TWA value of 52 mg/m^3. The RfC was derived by adjusting the inhalation mouse study's 6 hour/day 5 day/week LOAEL of 52 mg/m^3 to a 24 hour/day 7 day/week value of 9.3 mg/m^3 and then dividing by an uncertainty factor of 3000 (10x intra species variability, 10x inter species extrapolation, 10x for a lack of a NOAEL, and 3x for data base deficiencies). On the other hand, the TLV recommendation of 52 mg/m^3 was based on reviewing human poisoning incidents and other animal studies, including the inhalation mouse study. For the purposes of using naphthalene as an indicator of inhalation risk concerns for workers exposed to creosote, EPA is using the inhalation route-specific LOAEL of 52 mg/m^3 with a target MOE of 300 (10x intra species variability, 10x inter species extrapolation, and 3x for a lack of a NOAEL). While EPA recognizes that the 24 hour/day 7 day/week adjustment to the RfC is not representative of a typical work day, uncertainty factors are warranted to account for inter species extrapolation and variability among workers. Therefore, a inhalation MOE of greater than 300 is considered to indicate no risk concern.

Carcinogenicity - Summary: The carcinogenicity data base for creosote as required by the Agency in the 1988 DCI consist of a six-month dermal oncogenicity study of creosote conducted in mice. Creosote in this study was tested both as an initiator (5 dermal applications per week for 2 weeks at doses of 500 μg/mouse, 25 mg/mouse, or 56 mg/mouse followed by TPA for 26 weeks) and as a promotor (DMBA as a positive initiator at 50 μg/mouse followed by twice weekly applications of creosote at the same doses as used for the initiation protocol). As an initiator, creosote did not produce any increase in incidence of benign tumors, but at the 25 and 50 mg doses, squamous cell carcinomas were observed in 2/30 mice at each dose. As a promotor in DMBA-initiated mice, creosote produced dose-related increases in skin papillomas, keratoacanthoma, squamous cell carcinoma, and basal cell carcinoma at the 25 and 50 mg doses.

Increases in these tumor types were also observed when creosote was used as both initiator and promotor. This study shows that creosote acts most effectively as a promotor but also functions as a "complete" carcinogen.

The Agency proposes to use benzo(a)pyrene as an indicator for carcinogenic potential of creosote, but is also examining new published data on carcinogenicity of creosote itself to determine whether these data will modify the current proposal. This approach has been discussed in the Hazard Profile section of this document.

Creosote Worker Exposure Study: Although there are issues with the analytical portion of this study, the Agency has relied heavily on this study to assess dermal and inhalation exposures and cancer and non-cancer risks to workers in creosote pressure treatment plants. A brief summary of this study was presented earlier.

An in-depth discussion of exposures (excluding naphthalene) can be found in the human exposure chapter, but a summary of our findings for application (handler) and post-application scenarios is presented here:

Handler Exposures and Risks

Handler Scenarios with Non-Cancer Dermal Risk Concerns (Short- and Intermediate- term Risk)

Short- and intermediate-term non-cancer dermal risks for handlers (mixing/loading applying liquids at a pressure treatment facility- treatment operators and treatment assistant) are not of concern (i.e. MOEs are > 100) with additional engineering controls utilized.

Handler Scenarios with Non-Cancer Dermal Risk Concerns (Long-term Risk)

A risk of concern (i.e. MOE < 300) was identified for the non-cancer long term dermal exposure of treatment operators mixing/loading/applying liquids at a pressure treatment facility (long-term MOE of 140) with engineering controls.

Handler Scenarios with Non-Cancer Inhalation Risk Concerns (Short-Term, Intermediate-Term, and Chronic Risk)

In addition to reporting creosote inhalation non cancer risks, naphthalene has been selected to indicate worker risk concerns. Naphthalene has been selected because it was detected in all samples for each of the 12 job classifications in the creosote worker exposure study. The geometric mean air concentrations of naphthalene for the 12 job classifications are reported in Table 2. Table 2 presents these air concentrations as a percent of the TLV value (i.e., worker air concentration / TLV air concentration). Although the measured naphthalene air concentrations in

the worker's breathing zone represents only from 0.1 to 2.5 percent of the TLV, EPA considers additional uncertainty factors in the risk assessment. Table 2 also presents MOEs as which indicate a risk concern for the creosote workers. The target MOE is 300. The MOEs range from the highest potential risk of 12 for the cylinder area loader helper (CH) to the lowest potential risk of 390 for the load-out area loader helper (LH) activity. The MOEs are estimated using the following equation:

MOE = (LOAEL 52 mg/m^3 x 6 hr/day mouse study) / (worker air conc mg/m^3 x 8 hr/day workday x (1 m^3/hour working breathing rate / 0.4 m^3/hour resting breathing rate)

where: 1 m^3/hour working breathing rate represents for light activity; and
0.4 m^3/hour resting breathing rate to account for the fact that the mouse was "at rest" during the toxicity testing.

Table 2. Naphthalene Air Concentrations as an Indicator of Creosote Risks.

Job Classification [a]	Naphthalene Air Conc.(mg/m^3) Geo Mean (range) [b]	% of TLV [c]	MOE (Target 300) [d]
Cylinder area loader helper (CH)	1.291 (0.0794 to 5.918) n=10	2.5	12
Oil unloader (OU)	0.896 (0.701 to 1.399) n=5	1.7	17
Test borer (TB)	0.778 (0.514 to 1.648) n=5	1.5	20
Water treatment system operator (WO)	0.763 (0.500 to 1.987) n=5	1.5	20
Cylinder area loader operator (CLO)	0.596 (0.105 to 2.696) n=14	1.1	26
Treating operator (TO)	0.595 (0.133 to 2.624) n=14	1.1	26
Load-out area forklift operator (LLO (F))	0.433 (0.0750 to 1.259) n=5	0.8	36
Drip pad labor (DP)	0.255 (0.142 to 0.874) n=4	0.5	61
Load-out area loader operator (LLO)	0.138 (0.0282 to 1.540) n=14	0.3	110
Checker (CK)	0.083 (0.0308 to 0.268) n=5	0.2	190
Load-out area loader helper (LH)	0.04 (0.0269 to 0.0612) n=4	0.1	390
Treating assistant (TA)	0.346 (0.117 to 0.575) n=4	0.7	45

a Job classifications are based on the descriptions provided in MRID No. 453234-01).
b Geometric mean air concentration are used to estimate MOEs from MRID No. 453234-01.
c % TLV = (air conc mg/m3 / TLV 52 mg/m3) * 100.
d MOE = (LOAEL 52 mg/m3 x 6 hr/day mouse study) / (air conc mg/m3 x 8 hrs/day working x (1 m3 work activity / 0.4 m3 resting))

Short-term, intermediate-term, and long-term non-cancer inhalation risk concerns have been identified for the following scenarios (based upon calculated inhalation MOEs of less than 100:

a. Treatment operators (MOE = 10, based upon the Creosote Council's worker exposure study);

b. Treatment assistants (MOE = 17, based upon the Creosote Council's worker exposure study);

Handler Cancer Risks from Dermal and Inhalation Exposures to Creosote

The Agency has determined that all of the handler scenarios exceed the 1E-04 cancer risk levels. Therefore, all of the handler scenarios are expected to pose a risk concern.

Note that the Agency has adjusted cancer risk calculations by factors of 0.005 and 0.01. This was done because:

a. The cancer risk assessment is based upon benzo(a)pyrene, a component found in creosote formulations; and

b. Available information indicates that benzo(a)pyrene occurs as a component in creosote at levels of 0.5%. However, in order to provide a conservative assessment EPA has assumed that levels of benzo(a)pyrene may occur from 0.5% to 1% of total creosote formulations.

Even with use of the 0.005 and 0.01 adjustment factors the 1E-04 cancer risk level of concern is exceeded.

Post-application Exposures and Risks

Post-Application Scenarios with Non-Cancer Dermal Risk Concerns (Short-Term Risk)

Short-term non-cancer dermal risk concerns have been identified for the following scenarios (based upon calculated dermal MOEs of less than 100 - see Table 7 of Human Exposure Chapter):

a. Oil unloaders (MOE = 93 , based upon the Creosote Council's worker exposure study).

Note: Exposure data were not available for assessing short-term non-cancer risks for the following two scenarios:

a. Railroad worker; and

b. Pole installer.

Post-Application Scenarios with Non-Cancer Dermal Risk Concerns (Intermediate-Term Risk)

Intermediate-term non-cancer dermal risk concerns have been identified for the following scenarios (based upon calculated dermal MOEs of less than 100 - see Table 7 of Human Exposure Chapter):

a. Cylinder area loader helpers (MOE = 62 , based upon the Creosote Council's worker exposure study);

b. Checkers (MOE = 61, based upon the Creosote Council's worker exposure study);

c. Oil unloaders (MOE = 43 based upon the Creosote Council's worker exposure study)

Note: Exposure data were not available for assessing short-term non-cancer risks for the following two scenarios:

a. Railroad worker; and

b. Pole installer.

Post-Application Scenarios with Non-Cancer Dermal Risk Concerns (Chronic Risk)

Chronic non-cancer dermal risk concerns have been identified for the following scenarios (based upon calculated dermal MOEs of less than 300 - see Table 7 of Human Exposure Chapter):

a. Cylinder area loader operators (MOE = 160 based on the Creosote Council's worker exposure study);

b. Cylinder area loader helpers (MOE = 78 based on the Creosote Council's worker exposure study);

c. Checkers (MOE = 76 based on the Creosote Council's worker exposure study);

d. Drip pad laborers (MOE = 180 based on the Creosote Council's worker exposure study);

e. Load-out area forklift operators (MOE = 230 based on the Creosote Council's worker exposure study);

f. Oil unloaders (MOE = 54 based on the Creosote Council's worker exposure study);

h. Test borers (MOE = 130 based on the Creosote Council's worker exposure study);

Note: Exposure data were not available for assessing short-term non-cancer risks for the following two scenarios:

a. Railroad worker; and

b. Pole installer.

Post-Application Scenarios with Non-Cancer Inhalation Risk Concerns (Short-Term, Intermediate-Term, and Chronic Risk)

Short-term, intermediate-term, and chronic non-cancer inhalation risk concerns have been identified for all post-application scenarios for which there are data (based upon calculated inhalation MOEs of less than 100 - see Table 7 of Human Exposure Chapter):

a. Cylinder area loader operators (MOE = 8 based on the Creosote Council's worker exposure study);

b. Cylinder area loader helpers (MOE = 4 based on the Creosote Council's worker exposure study);

c. Checkers (MOE = 27 based on the Creosote Council's worker exposure study);

d. Drip pad laborers (MOE = 19 based on the Creosote Council's worker exposure study);

e. Load-out area loader operators (MOE = 19 based on the Creosote Council's worker exposure study);

f. Load-out area loader helpers (MOE = 65 based on the Creosote Council's worker exposure study);

g. Load-out area forklift operators (MOE = 10 based on the Creosote Council's worker exposure study);

h. Oil unloaders (MOE = 7 based on the Creosote Council's worker exposure study);

i. Test borers (MOE = 8 based on the Creosote Council's worker exposure study); and

j. Water treatment system operators (MOE = 11 based on the Creosote Council's worker exposure study).

Note: Exposure data were not available for assessing short-term non-cancer risks for the following two scenarios:

a. Railroad worker; and

b. Pole installer.

Post-Application Cancer Risks from Dermal and Inhalation Exposures to Creosote

The Agency has determined that all of the post-application scenarios exceed the 1E-04 cancer risk levels. This is based upon calculated dermal and inhalation residues from the Creosote Council's worker exposure study. Therefore, all of the post-application scenarios are expected to pose a risk concern.

Note that the Agency has adjusted cancer risk calculations by factors of 0.005 and 0.01. This was done because:

a. The cancer risk assessment is based upon benzo(a)pyrene, a component found in creosote formulations; and

b. Available information indicates that benzo(a)pyrene occurs as a component in creosote at levels of 0.5%. However, in order to provide a conservative assessment the Agency has assumed that levels of benzo(a)pyrene may occur from 0.5% to 1% of total creosote formulations.

Even with use of the 0.005 and 0.01 adjustment factors the 1E-04 cancer risk level of concern is exceeded.

Post-Application Non-Occupational (Residential) Scenarios

Potential post-application, non-occupational exposure scenarios likely include the following:

(1) Incidental ingestion and dermal contact with soil contaminated with creosote (e.g., soil contaminated by creosote-treated telephone poles) (child);

(2) Dermal contact with pressure treated wood products (e.g., utility poles, railroad ties used in home settings, posts) (adult); and

(3) Hand-to-mouth and dermal contact with industry pressure treated wood products (e.g., utility poles, railroad ties used in home settings, posts) (child).

However, adequate data are not available to assess these post-application exposures and risks.

Risk Mitigation

The majority of the calculated non-cancer and cancer risks are based upon the results of the Creosote Council II's 2001 worker exposure study which examined workers under actual creosote use conditions in wood treatment plants. Since each NAFTA partner (PMRA and CAL-DPR) has questions and issues associated with this study (e.g., analytical issues), further discussion among NAFTA partners, as well as with the Creosote Council II and study authors, is required to determine if there are any appropriate risk mitigation measures that can be taken to reduce non-cancer and cancer risks. Additionally, PMRA has indicated that they have videotapes from several of the sites studied; NAFTA partners have view of these tapes to assist in identifying any further risk mitigation measures that could be taken.

Data Gaps, Uncertainties, and Limitations

Data Gaps

1. Occupational Exposures: Although the Creosote Council II submitted a worker exposure study which addresses worker exposures in creosote pressure treatment plants, no data are available to assess railroad workers and utility pole installers.

2. Non-occupational (Residential) Exposures: Data are not adequate to characterize non-occupational (residential) post-application exposures.

Uncertainties/Limitations With The Occupational Handler and Post-Application Data

Issues with the Creosote Council II's worker exposure study (MRID 45323401):

a. The study sponsors made no attempt to relate inhalation levels found for PNAs and CTPVs to "total creosote" -- a significant weakness with the study;

b. There were inconsistencies in raw data and examples provided by the study authors: e.g., inhalation raw data did not reflect data found in bar graphs;

c. Air samplers did not show quantifiable levels for several of the PNAs monitored: (e.g., benzo(a)pyrene was not detected in any of the worker samples);

d. Inhalation field fortification percent recoveries for CTPVs were poor: overall recoveries ranged from 51 % - 57%.

Uncertainties/Limitations With Agency Cancer Risk Estimates

A specific quantitative cancer assessment on the carcinogenicity of creosote has not been performed by the Agency, but a cancer potency factor exists for one of the components of creosote, benzo(a)pyrene, with a Q1* value of $7.3(mg/kg/dy)^{-1}$. The Agency proposes to use the risk assessment for benzo(a)pyrene as an indicator for carcinogenic potential of creosote.

Considering the above, EPA adjusted creosote cancer risk calculations by factors of 0.005 and 0.01. This was done because:

a. The cancer risk assessment is based upon benzo(a)pyrene, a component found in creosote formulations; and

b. Available information indicates that benzo(a)pyrene occurs as a component in creosote at levels of 0.5%. However, in order to provide a conservative assessment the Agency assumed that levels of benzo(a)pyrene may occur from 0.5% to 1% of total creosote formulations.

However, it should be noted that although corrections to cancer risk estimates were made, data from the worker exposure study were not provided on the actual amount of benzo(a)pyrene found as dermal residues. Further, in this study all inhalation samples of benzo(a)pyrene were found to be at levels below the Level of Detection (LOD). These factors, therefore, increase the uncertainty of the cancer risk assessment.

Aggregate risk assessments

Acute Aggregate Risk

Under the current policy of the Office of Pesticide Programs, acute aggregate risk assessment determines the acute risk from combined dietary consumption of pesticide residues, separate from residential exposures (Health Effects Division, Standard Operating Procedure 97.2, April 1998). In the case of creosote, an acute aggregate (food + water) risk estimate was not performed for creosote. Creosote is not registered for any food use, and it has also been determined that creosote is not likely to impact the diet or drinking water.

Short- and Intermediate-Term Aggregate Risks

Aggregate short and intermediate term risk assessments are designed to provide estimates of risk likely to result from exposures to the pesticide or pesticide residues in food, water, and from residential (or other non-occupational) pesticide uses. Due to the lack of exposure through food or water, short and intermediate term aggregate risks were not performed. Residential exposures to creosote residues may occur, but data are not available to assess these risks.

Chronic (Non-Cancer) Aggregate Risk

Based on the lack of potential for chronic exposure to creosote through food and water, a chronic (non-cancer) aggregate risk assessment was not performed.

References

MRID	REFERENCE
453234-01	Creosote Council II, 2001. "Assessment of Potential Creosote Inhalation and Dermal Exposure Associated with Pressure-Treatment of Wood with Creosote." Submitted by John H. Butala, Creosote Council II. Field work by Mark G. Bookbinder, Ph.D, c/o American Agricultural Services Inc. Analytical work by Bert Clayton, EN-CAS Laboratories and Stephanie Guilyard, USX Engineers and Consultants.
None	Agency for Toxic Substances and Disease Registry (1995): Toxicological Profile for Polycyclic Aromatic Hydrocarbons. U.S. Department of Health and Human Services: Public Health Service.
None	Agency for Toxic Substances and Disease Registry (2002): Toxicological Profile for Creosote (update). U.S. Department of Health and Human Services: Public Health Service.
None	Butala, J.H. 1999. Creosote Council II memorandum with attachment to Nader Elkassabany, U.S. Environmental Protection Agency, Antimicrobials Division. February, 1999.
None	Murata et al. 1993. Chronic Toxicity and Carcinogenicity Studies of 1-methylnapthalene in B6C3F1 mice. Fundam Appl. Toxicol. 21(1): 1993.
None	McMahon, Timothy F. 1999. Creosote: Report of the Hazard Identification Assessment Review Committee. May, 1999. HED document no. 013375. Unpublished.
None	National Toxicology Program. TR 410. Toxicology and Carcinogenesis Studies of Naphthalene in B6C3F1 Mice (Inhalation Studies).
None	National Toxicology Program. TR 500. Toxicology and Carcinogenesis Studies of Naphthalene in F344/N Rats (Inhalation Studies).
None	Nesnow et al. 1998. Mechanistic relationships between DNA adducts, oncogene mutations, and lung tumorigenesis in strain A mice. Exp. Lung Res. 24(4): 1998.
None	USEPA, 1984: Wood Preservative Pesticides: Creosote, Pentachlorophenol, Inorganic Arsenicals. Position Document 4.
None	USEPA, 1997. FIFRA Science Advisory Panel. A Set of Scientific Issues Being Considered by the Agency to Discuss and Evaluate the Inhalation Risk

Assessments and the Combining of Margins of Exposure. Transmittal of the Final Report of the FIFRA Scientific Advisory Panel Meeting for March 19 and 20, 1997. April 28, 1997.

None Whalen, John E.vand Hugh M. Pettigrew. Inhalation Risk Characterizations and the Aggregate Risk Index (ARI). USEPA. Health Effects Division. November 25, 1998.

None York, Raymond G. (1994): Developmental Toxicity Study in New Zealand White Rabbits. Study conducted by IRDC, Mattawan, MI for Koppers Inductries, Pittsburgh, PA. Report no. 672-002. Unpublished.

None York, Raymond G. (1995): Two Generation Reproduction/Fertility Study in Rats. Study conducted by IRDC, Mattawan, MI for Koppers Inductries, Pittsburgh, PA. Report no. 672-006. Unpublished.

43032101 North American P1/P13 Creosote: Acute Oral Toxicity Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032102 North American P1/P13 Creosote: Acute Dermal Toxicity Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032103 North American P1/P13 Creosote: Acute Inhalation Toxicity Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032104 North American P1/P13 Creosote: Eye Irritation Study in Rabbits. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032105 North American P1/P13 Creosote: Primary Dermal Irritation Test in Rabbits. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032106 North American P1/P13 Creosote: Dermal Sensitization Study (Buehler) in the Albino Guinea Pig. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032301 North American P2 Creosote: Acute Oral Toxicity Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032302 North American P2 Creosote: Acute Dermal Toxicity Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished.

43032303 North American P2 Creosote: Acute Inhalation Toxicity Evaluation in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032304 North American P2 Creosote:Eye Irritation Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032305 North American P2 Creosote: Primary Dermal Irritation Test in Rabbits.Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43032306 North American P2 Creosote: Dermal Sensitization Study (Buehler) in the Albino Guinea Pig. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Unpublished. HED document no. 011033.

43601001 North American P1/P13 Creosote: Thirteen Week Subchronic Inhalation Toxicity Study on North American P1/P13 Creosote CTM in Rats: Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Report No. 671-016 (1995). Unpublished.

43600901 North American P2 Creosote: Thirteen Week Subchronic Inhalation Toxicity Study on North American P2 Creosote CTM in Rats: Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Report No. 671-018 (1995). Unpublished.

43616101 North American P1/P13 Creosote: 90-Day Subchronic Dermal Toxicity Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Report No. 671-013 (1995). Unpublished.

43616201 North American P2 Creosote: 90 Day Subchronic Dermal Toxicity Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Report No. 671-014 (1993). Unpublished.

43584201 North American P1/P13 Creosote: Developmental Toxicity Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Report No. 671-020 (1995). Unpublished.

43584202 North American P2 Creosote: Developmental Toxicity Study in Rats. Study conducted by IRDC, Mattawan, MI for the Creosote Council II. Report No. 671-022 (1995). Unpublished.

44844401 A 6-Month Dermal Oncogenicity Study of Creosote in Mice. Study conducted by WIL Research Laboratories, Ashland, OH for Koppers Industries, Pittsburgh, PA. Report no. WIL-100005. Unpublished.

45323401 Creosote Council II, 2001. "Assessment of Potential Creosote Inhalation and Dermal Exposure Associated with Pressure-Treatment of Wood with Creosote." Submitted by John H. Butala, Creosote Council II. Field work by Mark G. Bookbinder, Ph.D, c/o American Agricultural Services Inc. Analytical work by Bert Clayton, EN-CAS Laboratories and Stephanie Guilyard, USX Engineers and Consultants.